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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/552,206

09/14/2006

Irina Velikyan

PH0333

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10/15/2009

GE HEALTHCARE, INC.

IP DEPARTMENT 101 CARNEGIE CENTER

PRINCETON, NJ 08540-6231

EXAMINER

PERREIRA, MELISSA JEAN

ART UNIT

PAPER NUMBER

1618

MAIL DATE

DELIVERY MODE

10/15/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/552,206	Applicant(s) VELIKYAN ET AL.	
	Examiner MELISSA PERREIRA	Art Unit 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 July 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

In view of the appeal brief filed on 7/13/09, PROSECUTION IS HEREBY REOPENED.

A new grounds of rejection set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

1. The new grounds of rejection has been made to clearly meet the limitation of the the anion exchanger comprising HCO_3^- as counterions in the instant claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 1,3-7 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maier-Borst et al. (GB 2056471A) in view of Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, 43, 1088-1093).
4. Maier-Borst et al. (GB 2056471A) discloses the method of obtaining ^{68}Ga by the separation of ^{68}Ga for its parent nuclide, germanium-68, with 5N, 0.5N HCl and water via passing the eluant from a series of a generator column (in HCl) into an anion exchanger comprising quaternary ammonium groups incorporated in a matrix of styrene (in H_2O) and divinylbenzene and washing the anion exchanger with water (example 6; p4, lines 44-48). Maier-Borst et al. does not disclose the anion exchanger comprising HCO_3^- as counterions.
5. Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, 43, 1088-1093) discloses strongly basic anion exchange resins which are quaternary ammonium salts having a polystyrene crosslinked with divinylbenzene base (Dowex 1 and 2) (p1088, paragraph 1). Dowex 1 and 2 are provided in various ionic forms, such as bicarbonate (table I; table II).
6. At the time of the invention it would have been obvious to one ordinarily skilled in the art that the anion exchange resin comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene may comprise the bicarbonate counterion as the bicarbonate provides for a minimal amount of swelling and thus greater selectivity of the anion exchange resin (Wheaton et al. p1089, resin swelling).

7. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (WO03/059397A2) in view of Bottcher et al. (US 5,439,863) and further in view of Maier-Borst et al. (GB 2056471A) and Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, 43, 1088-1093).

8. Griffiths et al. (WO03/059397A2) discloses the method of producing a ^{68}Ga -radiolabeled complex/ ^{68}Ga -labeled targeting agent for use in PET detection (p4, paragraph 2; p9, paragraph 1). The method of obtaining the ^{68}Ga involves eluting ^{68}Ga from a $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide based in-house generator. The ^{68}Ga is eluted from the titanium dioxide generator, which can be fitted with an anion-exchange membrane/Q5F cartridge (p14, paragraph 1) with acidic solution, such as 0.5-1N HCl (p7, paragraph 3; p8, paragraph 2; p12, paragraph 1). The method of producing a radiolabeled gallium complex involves reacting the solution of a peptide labeled macrocyclic chelate with the ^{68}Ga diluted from the $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide generator (p14, paragraph 1). The chelate-targeting agent conjugates can be compounded into kits that are ready to use and accept the ^{68}Ga elute (p8, paragraph 3). The macrocyclic-chelating agent, such as DOTA or NOTA may be linked to a peptide that can target the site of a disease, thus generating a bifunctional chelating agent comprising a targeting vector which will be site-specific (p9, paragraph 1; p11, paragraphs 1 and 2).

9. Griffiths et al. does not disclose the preparation of the chelate-targeting agent conjugates via microwave acceleration. Griffiths et al. also does not disclose an anion exchanger comprising HCO_3^- or more specifically one comprising an amine functional groups or one based on polystyrene-divinylbenzene.

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10. Bottcher et al. (US 5,439,863) discloses the preparation of metal complex salts via microwave irradiation (column 3, line 44-46). The complexes are prepared from metal ions, such as those of the second and third main group, not excluding gallium and multitoothed chelating ligands that occupy more than one coordination site on the central metal atom (column 3, lines 55-59; column 4, lines 44-46). The ligands of the disclosure may include those with dioxime (N and O containing), etc. groups (column 5, lines 20-24). The use of microwave as the high-energy input allows for a continuous conversion, single-stage reaction with short reaction time and ease of separation of the formed complexes (column 4, line 19; column 5, lines 66+; column 6, lines 1-5).

11. Maier-Borst et al. (GB 2056471A) discloses the separation of ^{68}Ga for its parent nuclide, germanium-68, with 5N HCl and water via passing the eluant from a generator column into an anion exchanger comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene and washing the anion exchanger with water (p4, lines 44-48).

12. Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, 43, 1088-1093) discloses strongly basic anion exchange resins which are quaternary ammonium salts having a polystyrene crosslinked with divinylbenzene base (Dowex 1 and 2) (p1088, paragraph 1). Dowex 1 and 2 are provided in various ionic forms, such as bicarbonate (table I; table II).

13. At the time of the invention it would have been obvious to produce a ^{68}Ga -DOTA-peptide complex for use as a PET tracer via the production of ^{68}Ga from a $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide generator as disclosed by Griffiths et al. The microwave synthesis

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technique for the method of producing metal-chelate complexes was known by Bottcher et al. thus, it would have been obvious to utilize the microwave acceleration technique for a faster, more reproducible preparation of the ^{68}Ga -DOTA-peptide complex, such as that of Griffiths et al. to generate a complex useful in the treatment or diagnosis of tumours with minimal side product formation. Microwave acceleration techniques have been utilized since the 1980's in a number of production methods for radioactive precursors and radiotracers labeled with positron-emitting nuclides. The microwave method is mostly associated with shortened reaction times and encompasses the microwave conditions of the instant claims. Since the microwave technique was known in the art (Bottcher et al.) one would have a reasonable expectation of success for preparing radiotracer via labeling reactions with this improved microwave technique.

14. It is known in the prior art to add a chelating agent, such as EDTA to elute ^{68}Ga from an aluminum oxide exchanger. The disadvantage of forming the ^{68}Ga -EDTA complex is that the complex has to be destroyed before further processing to obtain radiopharmaceutical agents which is time-consuming and expensive (see Maier-Borst et al. p1, lines 10-16). It would have been obvious to one ordinarily skilled in the art to utilize the anion exchanger of Maier-Borst et al. to separate ^{68}Ga from its parent nuclide since no chelating agent is required for separation, as Maier-Borst et al. is drawn to the same method of the separation of ^{68}Ga from ^{68}Ge without the use of an EDTA chelating agent. Thus, it would have been predictable and favorable to utilize the anion exchanger of Maier-Borst et al. to avoid the extra step of destroying a ^{68}Ga -EDTA for further processing to obtain radiopharmaceutical agents.

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15. At the time of the invention it would have been obvious to one ordinarily skilled in the art that the anion exchange resin comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene may comprise the bicarbonate counterion as the bicarbonate provides for a minimal amount of swelling and thus greater selectivity of the anion exchange resin (Wheaton et al. p1089, resin swelling).

Response to Arguments

16. Applicant's arguments filed 7/13/09 have been fully considered but they are not persuasive.

17. Applicant asserts that Bottcher et al. does not teach microwaves are preferred over using ultrasound or laser beams as inputs of energy.

18. The limitation of using microwaves to form the complexes does not need to be exemplified. Bottcher et al. discloses the preparation of metal complexes (metal-multitoothed chelating ligand complex) via microwave irradiation which allows for a continuous conversion, single-stage reaction with short reaction time and ease of separation of the formed complexes (Bottcher et al. column 4, line 19; column 5, lines 66+; column 6, lines 1-5). Bottcher et al. explicitly states microwave as an energy input and thus it is obvious to one skilled in the art that microwave is a viable energy input. Griffiths et al. teaches of the preparation of a metal-NOTA/DOA ligand complex (i.e. ⁶⁸Ga-radiolabelled complex) and since the microwave technique was known in the art (Bottcher et al.) for the preparation of such metal-multitoothed chelating ligand complexes one would have a reasonable expectation of success for preparing the

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metal-ligand complex, ^{68}Ga -radiolabelled complex, of Griffiths et al. via with the faster and more efficient microwave technique of Bottcher et al.

19. Applicant asserts that Bottcher et al. does not disclose, teach or suggests using a microwave oven as disclosed in the present invention to enhance or improve efficiency and reproducibility of the neutral metal complex salt formation.

20. Bottcher et al. explicitly states microwave as an energy input and thus it is obvious to one skilled in the art that microwave is a viable energy input. Bottcher et al. teach that microwave allows for a continuous conversion, single-stage reaction with short reaction time and ease of separation of the formed complexes (Bottcher et al. column 4, line 19; column 5, lines 66+; column 6, lines 1-5). The instant claims recite "microwave activation" and do not provide any active steps over standard microwave activation, therefore the microwave activation of Bottcher et al. encompasses that of the instant claims and is capable of the same functions, such as to enhance or improve efficiency and reproducibility and has the same properties.

21. Applicant asserts that the objective of Maier-Borst et al. was to synthesize an anion exchange resin for the separation of gallium-68 from germanium-68 thus avoiding the use of EDTA for elution as it was done before the 1980's.

22. The instant claims are drawn to the method of obtaining ^{68}Ga from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator with an anion exchanger, such as polystyrene-divinylbenzene and a dilute HCl solution. The reference of Maier-Borst et al. is drawn to process for preparing an ion (anion)-exchanger which encompasses the anion exchange resin of the instant claims and further is drawn to the method of obtaining ^{68}Ga from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator

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with the anion exchanger, such as styrene and divinylbenzene and a dilute HCl solution (p1, lines 59-63) and therefore the method of Maier-Borst et al. encompasses the method of the instant claims and is capable of the same functions (i.e. labeling efficiency, etc.) and has the same properties.

23. The assertion with regard the preconcentration of gallium-68 appears to be unexpected results but was not provided in the proper declaration with a comparison of the closest prior art. Also, the instant claims do not provide the limitations of a preconcentration procedure which is asserted as necessary by the applicant.

Double Patenting

24. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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25. Claims 1,2 and 6-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 10/552,134. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of producing a ^{68}Ga -radiolabeled complex of the instant claims encompasses the method of producing a radiolabeled gallium complex of the copending Application No. 10/552,134 since the method steps are identical. Both inventions involve reacting a ^{68}Ga radioisotope with a macrocyclic or bifunctional chelating agent via microwave. The inventions also include a targeting moiety that may be bound to the chelating agent for site-directed localization. The generation of the ^{68}Ga radioisotope of both applications involves eluting the ^{68}Ga from a $^{68}\text{Ge}/^{68}\text{Ga}$ titanium dioxide generator followed by purification of the ^{68}Ga eluate via a strong anion exchanger. Therefore, the resulting radiolabeled gallium complex of the instant claims is obviously generated via the synthesis and isolated and would encompass that radiolabeled gallium complex of the copending application.

26. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

27. Claims 1,2 and 6-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 7-13 of copending Application No. 11/358,681. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method for producing a

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^{68}Ga -radiolabelled complex of the instant claims encompasses the method for labeling synthesis of radiolabeled gallium complex of 11/358,681. The method of the instant claims includes the method of obtaining ^{68}Ga by contacting the eluate from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator which is also disclosed in the method of 11/358,681. The macrocyclic chelating agents (DOTA), the generator column (titanium dioxide), the strong anion exchangers and the use of microwave activation for the preparation are identical for the instant claims and copending Application No. 11/358,681. The species of targeting vector protein, such as hEGF of 11/358,681 anticipate the genus of targeting vector proteins of the instant claims. Therefore, the resulting radiolabeled gallium complex of the instant claims is obviously generated and isolated via the synthesis and would encompass that radiolabeled gallium complex of the copending application.

28. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618